Incomplete Revascularization and Long-Term Survival after Coronary Artery Bypass Graft Surgery. Do extent of incompleteness and off-pump surgery play a role?

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Abstract

Background: We sought to investigate the impact of incomplete revascularization (IR) on long-term survival after isolated coronary artery bypass grafting (CABG) by analysing 20 years single institution data. The emphasis of this study is large sample size, focus on the extent of IR and long term follow-up.

Methods and Results: A total of 13,701 patients with multivessel disease undergoing CABG were included in the analysis. All patients received left internal thoracic artery (LITA) to the left anterior descending artery (LAD) territory. IR of the right coronary artery (RCA) and/or the circumflex (CX) artery was defined as at least one diseased arterial territory incompletely revascularized. Overall 3,107 (22.7%) patients received IR. After propensity score matching, IR did not increase all cause death in the overall group (HR 1.09; 95%CI 0.96-1.22; P=0.17). However, when both RCA and CX artery were incompletely revascularized, late survival was significantly lower (HR 2.15; 95%CI 1.57-2.93). IR was associated with a higher risk of death after off-pump (HR 1.26; 95%CI 1.05-1.49) regardless the extent of IR. After on-pump, IR significantly affected survival only when both RCA and CX artery only were incompletely revascularized (HR 2.32; 95%CI 1.27-4.22).

Conclusions: The present analysis showed that the impact of IR on survival is marginal when the procedure is performed with the use of cardiopulmonary bypass while IR after off-pump CABG remains associated with significantly lower survival. The worst survival rates are observed when both RCA and CX artery remain incompletely revascularized.

Despite complete revascularization (CR) has long been considered the goal of coronary artery bypass graft (CABG) surgery [1] this is not always achieved due to procedural difficulties [2]. The impact of incomplete revascularization (IR) on long term survival remains uncertain [2,3]. No randomized controlled trial has ever tested whether CR is superior to incomplete revascularization (IR) and results from observational cohorts are conflicting [2-7]. What remains unclear is whether different degrees of IR can have different effect on survival. Moreover, patients who undergo IR are more likely to present multiple comorbidities and this could bias the data in favour of complete revascularization. Finally several comparisons between IR and CR strategies report mid-term results only [2,3] and longer follow-up might be necessary for IR to show its detrimental effect on survival [4].

We sought to investigate the impact of IR on long-term survival after isolated CABG by analysing 20 years single institution data. The emphasis of this study is large sample size, focus on the extent of IR and long term follow-up.

Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. We retrospectively analysed prospectively collected data from The National Institute for Cardiovascular Outcomes Research (NICOR) registry on 1 June 2015 for all isolated first time CABG procedures performed at the Bristol Heart Institute, Bristol United Kingdom from 1996 to April 2015. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required. Briefly, duplicate records and non-adult cardiac surgery entries were removed; transcriptional discrepancies harmonized; and clinical conflicts and extreme values corrected or removed. The data are returned regularly to the local units for validation.

Further details and definition of variables are available at http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets. During the study period, a total of 15,119 patients underwent first time isolated CABG; 931 subjects operated for single vessel disease were excluded; information on the use of cardiopulmonary bypass (on-pump vs off-pump) was not available in 487 cases which were excluded. A total of 13,701 subjects were included in the final analysis. All patients received left internal thoracic artery (LITA) to the left anterior descending artery (LAD) territory. The incidence of incomplete revascularization (IR) of the right coronary artery (RCA) and/or the circumflex (CX) artery was defined as at least one diseased arterial territory incompletely revascularized. Overall 3,107 (22.7%) and 10,594 patients (78.8%) received IR and CR respectively.

Pre-treatment variables

The effect of OPCAB on outcomes of interest was adjusted for the following pre-treatment variables including: age, gender, body mass index (BMI); New York Heart Association grade III or IV; previous myocardial infarction (MI) and MI within 30 days, previous percutaneous coronary intervention (PCI); diabetes mellitus (DM) on oral treatment or on insulin; chronic obstructive pulmonary disease (COPD); current smoking; serum creatinine ≥200 mmol/l, previous CVA; peripheral vascular disease (PVD); left main disease (LMD); number of vessel diseased; left ventricular ejection fraction (LVEF) between 30% and 49%; LVEF less than 30%; non elective admission, emergent/salvage operation; preoperative IABP; off-pump surgery; use of additional arterial grafts and eras of surgery.

Categorical variables are presented as frequencies and percentages and continuous variables as mean±standard deviation. Survival curves were constructed using Kaplan-Meier estimates. To reduce the effect of treatment selection bias and potential confounding, we adjusted for differences in baseline characteristics by propensity score (PS) matching [8].

A PS was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with treatment type (IR vs CR) as a binary dependent variable. The resulting propensity score represented the probability of a patient undergoing IR. Pairs of patients undergoing IR and CR were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS (nonrandom R package). The quality of the match was assessed by comparing selected pre-treatment variables in propensity score– matched patient using the standardized mean difference (SMD), by which an absolute standardized difference of greater than 10% is suggested to represent meaningful covariate imbalance. Analytic methods that account for the within-pair homogeneity and clustering effect related to individual surgeon were used for the estimation of the treatment effect in the matched sample. Cox proportional hazards regression stratified for PS matched pairs was used to investigate the effect of IR on survival (survival R package). IR of the RCA and the CX artery was investigated separately. Potential effect modifiers (interaction terms) examined were age<70 vs ≥70 years; female vs male; diabetes mellitus vs no diabetes; LVEF<0.50 vs ≥50%; creatinine >200mmol/l vs creatinine <200mmol/l; off-pump vs on-pump; 3-vessel vs 2-vessel disease; left main disease vs no left main disease; use of multiple arterial conduits versus single arterial revascularization plus saphenous vein grafts. All p-values <0.05 were considered to indicate statistical significance. The Schoenfeld residuals test was used to test the independence between residuals and time and hence to test the proportional hazards assumption in Cox models (all P values were >0.05). All statistical analysis were performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 3107 (22.7%) patients received IR. Patients' characteristics before and after PS matching are reported in Table 1. Patients receiving IR were more likely to have three vessel disease, receive off-pump surgery. We also find a trend towards a higher incidence of LVEF less than 30% and PVD in the IR group. Patients receiving CR were more likely to receive multiple arterial grafting. The overall number of grafts was significantly lower in the IR group. PS matching selected 3107 matched pairs comparable for all the baseline characteristics. Table 2 summarizes number of grafts performed with relative targets in the CR and IR groups. Before matching survival rates at 5, 10 and 15 years were 86.4±0.6% versus 89.3±0.3%, 69.9±0.9% versus 74.7±0.5% and 51.5±1.4% versus 57.2±0.8% in the IR and CR groups respectively (HR 1.24; 95%CI 1.15-1.34; P<0.001). Survival rates at 5, 10 and 15 years in the CR matched group were 88.6±0.6% 72.3± 1.0% and 51.8±1.5% with no significant difference compared to the IR group (HR 1.09; 95%CI 0.96-1.22; P=0.17; Figure 1 left). When the analysis was conducted according to the extent of IR, we found that incompletely revascularized RCA only (HR 1.06; 95%CI 0.95-1.19) or incompletely revascularized CX artery only did not increased the risk of death (HR 1.04; 95%CI 0.90-1.19). However, when both RCA and CX artery were incompletely revascularized, late survival was significantly lower (HR 2.15; 95%CI 1.57-2.93; Figure 1 right).

Subgroup analysis (Figure 2) showed that IR was associated with a higher risk of death after off-pump (HR 1.26; 95%CI 1.05-1.49) but not on-pump surgery (HR 0.91; 95%CI 0.75-1.1; interaction P=0.01). In case of off-pump surgery, incompletely revascularized RCA only (HR 1.20; 95%CI 1.02-1.41), incompletely revascularized CX artery only (HR 1.20; 95%CI 1.01-1.44) and concomitant incompletely revascularized RCA and CX artery (HR 2.14; 95%CI 1.48-3.09) were associated with poorer survival. In case of on-pump surgery, when both RCA and CX artery were incompletely revascularized survival was significantly lower (HR 2.32; 95%CI 1.27-4.22), but IR did not significantly affect survival in case of incompletely revascularized RCA only (HR 0.96; 95%CI 0.82-1.12) or incompletely revascularized CX artery only (HR 0.90;95%CI 0.73-1.10) (Figure 3).

Discussion

The main finding of the present study is that the detrimental effect of incomplete revascularization after CABG on survival is more relevant in subjects undergoing off-pump when compared to on-pump surgery. During on-pump surgery, IR affects survival only if both RCA and CX artery are incompletely revascularized.

CR is a major goal in CABG based on the long-existing principle that CR is superior to IR regrading long-term survival to early and long-term survival [1]. The association between CR and lower risk for subsequent cardiovascular events may be causal. CR may improve clinical outcomes by reducing or eliminating myocardial ischemia, which has been linked to worse prognosis, especially when large [9,10]. However, IR may be a surrogate marker for higher burden of comorbidities and more advanced coronary artery disease that is less amenable to revascularization [3]. In the latter case, IR per se might not be particularly relevant on patients' outcome. The likelihood of achieving CR with either CABG or percutaneous coronary intervention, ideally estimated by a heart team approach, should influence the decision to proceed with CABG or PCI [2,11]. With this approach in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial [2], the rates of IR were 43.3% for PCI and 36.8% for CABG, which compares favorably with historical cohorts [12], while still highlighting the procedural complexity of achieving CR during CABG. Interestingly, in the SYNTAX trial, IR was found to be associated with poorer outcomes in the PCI arm but not in the CABG arm [2]. It has been suggested the detrimental effect of IR in the CABG population might be mitigated by the presence of LITA to LAD graft [3] and the use of additional arterial grafts [13]. On the other hand, off-pump CABG has been consistently associated with a higher incidence of incomplete revascularization and a trend towards poorer survival [14-18]. The present analysis showed that IR is more relevant when occurs in off-pump CABG than on-pump CABG. Common reasons for IR are based on preoperative assessment (eg, nondominant diseased right coronary artery, non-vital myocardium, limited graft material), or more unexpected findings during the operation (ie, small target vessel, severely calcified artery). These conditions are anticipated to not have a major impact of outcomes. However, during off-pump CABG, surgeon ability plays a major role in determining the completeness of revascularization and vessels supplying large portion of viable myocardium can remain ungrafted.

We here focused on the prognostic impact of IR of circumflex and right coronary artery territory and we found that when performing LITA-to-LAD bypass, IR does not adversely affect survival unless both the circumflex or right coronary artery territory are incompletely revascularized. However, this was true only for patients undergoing on-pump surgery while the detrimental effect IR on survival was more relevant after off-pump CABG. Therefore, our findings support the hypothesis that IR during on-pump strongly different from IR during off-pump when good graftable vessels with large areas of viable myocardium remain untreated due to limited surgeon's ability [17,18].

A possible explanation for the lack of negative effect form IR during on-pump is that the progression in modern era with secondary pharmacological treatment could partially compensate surgical IR in diffuse distal CAD of the non-LAD territories. It has been suggested that the lower number of distal anastomoses might be compensated by the higher number of arterial grafts for non-LAD targets in IR patients [13]. However, this hypothesis has been recently challenged by mid-terms result of the Arterial Revascularization Trial (ART) that failed to show a significant benefit from using a second arterial graft for the CX territory [19]. Our results are in line with the ART trial and highlight the primary importance of completeness of revascularization in particular while performing off-pump CABG.

Limitations

There are some limitations of the present study. First, it was subject to all limitations inherent to a nonrandomized study, including potential selection bias regarding which patients underwent CR versus IR. This was partially addressed by using PS matching to minimize residual imbalance for measured variables, but we could not account for unmeasured factors and in particular for targets quality. The current data lacks a standardized, universal definition of what constitutes an IR procedure [2-4]. Gössl et al. [20] recently proposed a universal definition of IR using coronary angiography and fractional-flow reserve (FFR) data. Based on the previous work by Piljs et al. [21] regarding the excellent long-term outcomes of patients with intermediate stenosis and insignificant FFR and the observation that FFR-guided PCI in patients with multivessel coronary artery disease is superior to angiography-guided PCI, a definition of IR that includes anatomy and physiology seems intuitive. However, FFR was not available for the present analysis.

Conclusion.

The present analysis showed that the impact of IR on survival is marginal when the procedure is performed with the use of cardiopulmonary bypass while IR after off-pump CABG remains associated with significantly lower survival. The worst survival rates are observed when both RCA and CX artery remain incompletely revascularized. These results confirm that complete revascularization remains the main goal while performing off-pump CABG and that off-pump should be avoided if CR cannot be achieved.

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Figure Legends

Figure 1. Survival rates in propensity matched subjects receiving complete revascularization (CR) vs incomplete revascularization (IR) in the overall sample (left) and impact of incomplete revascularization in the right coronary artery (RCA) and circumflex artery (CX) territory (right).

Figure 2. Subgroup analysis of the effect of incomplete revascularization on mortality.

Figure 3. Impact of incomplete revascularization (IR) in the right coronary artery (RCA) and circumflex artery (CX) territory (right) when compared to complete revascularization (CR) in on-pump and off-pump surgery.

Supplementary Figure 1. Standardized mean difference before and after matching.

Table 1. Baseline characteristics before and after matching

	IR	CR	SMD	CR matched	SMD
	N=3107	N=10594		N=3107	
Age, mean (sd)	66.55 (9.47)	66.05 (9.27)	0.054	66.73 (8.95)	0.020
Female, n (%)	557 (17.9)	1866 (17.6)	0.008	549 (17.7)	0.007
BMI (mean (sd))	27.91 (4.53)	27.86 (4.42)	0.011	27.86 (4.61)	0.011
NYHA III-IV, n (%)	965 (31.1)	3090 (29.2)	0.041	966 (31.1)	0.001
MI 30 days, n (%)	589 (19.0)	2053 (19.4)	0.011	597 (19.2)	0.007
PCI, n (%)	182 (5.9)	545 (5.1)	0.031	192 (6.2)	0.014
DMO, n (%)	356 (11.5)	1089 (10.3)	0.038	329 (10.6)	0.028
DMI, n (%)	257 (8.3)	761 (7.2)	0.041	253 (8.1)	0.005
Smoking, n (%)	419 (13.5)	1377 (13.0)	0.014	419 (13.5)	<0.001
Cr>200mmol/l, n (%)	99 (3.2)	257 (2.4)	0.046	111 (3.6)	0.021
COPD, n (%)	267 (8.6)	795 (7.5)	0.040	273 (8.8)	0.007
CVA, n (%)	128 (4.1)	391 (3.7)	0.022	118 (3.8)	0.017
PVD, n (%)	358 (11.5)	1025 (9.7)	0.060	358 (11.5)	<0.001
LVEF31-49%, n (%)	731 (23.5)	2290 (21.6)	0.046	731 (23.5)	<0.001
LVEF ≤30%, n (%)	198 (6.4)	522 (4.9)	0.063	207 (6.7)	0.012
Non-elective, n (%)	1503 (48.4)	5054 (47.7)	0.013	1504 (48.4)	0.001
Emergent, n (%)	56 (1.8)	165 (1.6)	0.019	56 (1.8)	<0.001
Preop IABP, n (%)	45 (1.4)	155 (1.5)	0.001	44 (1.4)	0.003
NVD, n (%)			0.502		<0.001
2	383 (12.3)	3421 (32.3)		383 (12.3)	
3	2724 (87.7)	7173 (67.7)		2724 (87.7)	
LMD, n (%)	810 (26.1)	2829 (26.7)	0.014	826 (26.6)	0.012
OPCAB, n (%)	1751 (56.4)	4978 (47.0)	0.188	1729 (55.6)	0.014
MAG, n (%)	565 (18.2)	2462 (23.2)	0.125	533 (17.2)	0.027
Eras, mean (sd)	2004.92 (5.12)	2004.92 (5.28)	0.001	2004.98 (5.06)	0.012

Table 2. Number of grafts and targets in CR and IR groups.

	CR	IR	P
2-vessel disease, n	383	383	
N grafts, mean (sd)	2.18 (0.40)	1.56 (0.51)	<0.001
CX artery, n (%)	223 (58.2)	14 (3.7)	<0.001
RCA, n (%)	179 (46.7)	20 (5.2)	<0.001
3-vessel disease, n	2724	2724	
N grafts, mean (sd)	3.26 (0.47)	2.58 (0.62)	<0.001
CX artery, n (%)	2723 (100.0)	1761 (64.6)	<0.001
RCA, n (%)	2724 (100.0)	911 (33.4)	<0.001